

## B

## Abstract

### Long-term Efficacy and Durability of Lamivudine Therapy in Patients with Chronic Hepatitis B

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**Background/Aims:** It has been reported in patients with chronic hepatitis B, that the response rate of lamivudine therapy increases in proportion to the duration of the therapy. What was not well known was the durability of the therapeutic response after the cessation of lamivudine therapy. The aim of this study was to evaluate the long-term efficacy and durability of lamivudine therapy in patients with chronic hepatitis B. **Patients and Methods:** We retrospectively analyzed 73 patients with chronic hepatitis B who were treated with lamivudine 100 mg orally once daily and followed up for more than 12 months between April 1997 and March 1999. Sixty-three patients were initially hepatitis B e antigen (HBeAg) positive and Hepatitis B virus (HBV) DNA positive (group I). Ten patients were HBeAg negative and HBV DNA positive (group II). The responders were those who had negative conversion of HBV DNA and normalization of alanine aminotransferase (ALT). Treatment was stopped after HBeAg seroconversion in group I and after therapeutic response in group II. **Results:** The response rates of group I and group II were 68.3% and 70.0% at 12 months, respectively ( $P = \text{NS}$ ). In group I, cumulative HBeAg seroconversion rates at 1 year, 2 years, and 3 years were 30.2%, 38.8%, and 42.4%, respectively. The cumulative durability of response was higher in group I than in group II (64.6% vs. 33.3% at 1 year; 35.4% vs. 22.2% at 2 years;  $P = .079$ ). The cumulative durability of response was significantly higher in patients who received additional lamivudine therapy for more than 6 months after HBeAg seroconversion than for less than 6 months (90.0% vs. 40.0% at 1 year; 90.0% vs. 20.0% at 2 years;  $P = .013$ ). **Conclusions:** The long-term response to lamivudine therapy showed no difference between HBeAg-negative/HBV DNA-positive and HBeAg-positive patients. The HBeAg seroconversion rate increased in proportion to the duration of lamivudine therapy. The Continuation of treatment for more than 6 months after HBeAg seroconversion might increase the durability of response. (**Korean J Hepatol 2001;7:423-431**)

**Key Words:** Hepatitis/Viral/chronic Hepatitis B, Lamivudine, HBeAg seroconversion, Durability

◇ 2001 7 21 ; 2001 10 12 ; 2001 11 26

◇ Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; FHx, family history; HBV, hepatitis B virus; HIV, human immunodeficiency virus.

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가 , HBeAg

B

HBeAg

B

30-40%

HBeAg

1-3

가 , 4,5

1.

B

25-30%

1997 4 1999 5

6-8

B

HBeAg /HBV DNA B 12

73

9-11

73 HBeAg /HBV DNA B

( 1 )가 63 HBeAg /HBV DNA ( 2 )가 10 . 1

(nucleoside analogue)가 B

(Lamivudine, (-)- 2',3'-di-deoxy-3'-thiacytidine, 3TC) human immunodeficiency virus (HIV)

가 57 (90.5%)

가 6 (9.5%) , 2 B

가 6 (60.0%), 가

4 (40.0%) . lamivudine

3 HBV DNA 5 pg/mL

B

12-14

ALT 40 IU/L

HBeAg

2.5 mg/dL ,

70% ,

3.5 g/dL , , ,

15-18

HBeAg 가

19,20

HBeAg /HBV DNA B

HBeAg B

21

가

1.5 mg/dL , 11 g/dL ,

22

HBeAg B

3000 /mm<sup>3</sup> , 100,000 /mm<sup>3</sup>

23

37.7 ± 10.3 ( , 15-61 ) 1 37.2 ± 10.5 ( , 15-61 ), 2

가 40.8 ± 8.7 ( , 27-55 ) . 64:9

1 55:8, 2 9:1 . ALT

197 IU/L (43- 1422) 1 209 IU/L (43- 1422 IU/L), 2 176 IU/L (69- 957 IU/L)

24

25

B

HBV DNA 472 pg/mL

**Table 1.** Clinical Characteristics of Patients

Variables	Group I* (n = 63)	Group II** (n = 10)	Total (n = 73)
Age (years)	37.2±5.9	40.8±8.7	37.7±10.3
Sex (M: F)	55:8	9:1	64:9
Diagnosis			
Chronic hepatitis	57 (90.5%)	6 (60.0%)	63 (86.3%)
Compensated LC <sup>†</sup>	6 (9.5%)	4 (40.0%)	10 (13.7%)
ALT (IU/L)			
Median (range)	209 (43- 1422)	176 (69- 957)	197 (43- 1422)
HBV DNA (pg/mL)			
Median (range)	554.5 (5.1- 9600)	215.5 (13.1- 1750)	472 (5.1- 9600)
Previous IFN- therapy	19 (30.2%)	1 (10.0%)	20 (27.4%)
FHx <sup>‡</sup>	20 (31.7%)	2 (20.0%)	22 (30.1%)

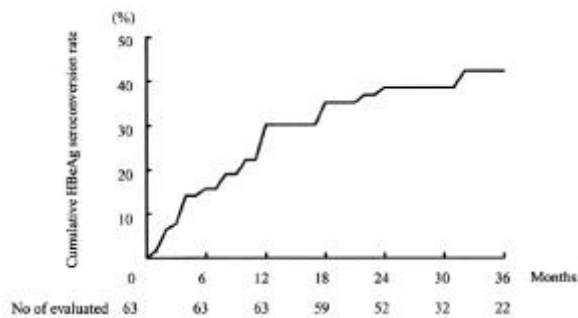
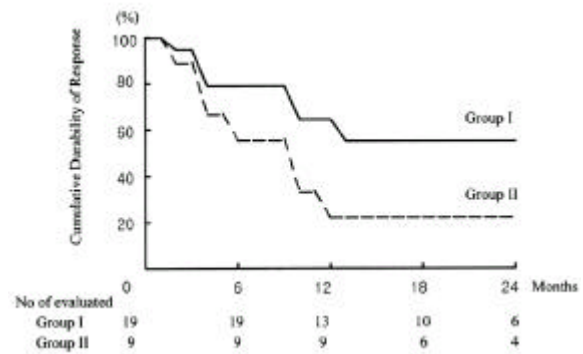
\*, HBeAg-positive/HBV DNA-positive chronic liver disease; \*\*, HBeAg-negative/HBV DNA-positive chronic liver disease; <sup>†</sup>, Compensated liver cirrhosis; <sup>‡</sup>, Family history of chronic hepatitis B virus infection.

(5.1- 9600 pg/mL) 1 565 pg/mL (5.1- 9600 pg/mL), 2 215.5 pg/mL (13.1- 1750 pg/mL) . 20 가 . 22 B 가 ( 1). HBeAg , anti-HBe , HBV DNA (<5 pg/mL), ALT (<40 IU/L) . 1 HBeAg , 2 HBV DNA 가 (>5 pg/mL) . 2. (28 ) 100 mg 1 (19 ) 15.5±6.4 ( , 6-28 ), 2 (9 ) 13.1±3.22 ( , 8-18 ) , 1 (19 ) 15.6±7 ( , 8-32 ), 2 (9 ) 21.6±8.7 ( , 12-40 ) . 가 , HBeAg B (19 ) (7 ) (12 ) 2-3 가 . . HBsAg, HBeAg, anti-HBs, anti-HBe enzyme immunoassay (Dade Behring, Malburg, Germany) , HBV DNA hybridization (Digene Diagnostic Inc, Bestivelle, MD, USA) . 3. SPSS (ver. 10.0) 95% . Fisher's exact test student's t- test Mann-Whitney U test HBV DNA가 (<5 pg/mL) ALT가 (<40 IU/L) . HBeAg (seroconversion)

**Table 2.** Comparison of the Clinical Characteristics Between HBeAg Seroconvertors and Non-seroconvertors in Patients with HBeAg-Positive Chronic Hepatitis B

Variables	Seroconvertors (n = 25)	Non-seroconvertors (n = 38)	<i>p</i>
Age (years)	33.8 ± 10.6	39.4 ± 9.9	< 0.05
Sex (MF)	22:3	33:5	NS
Diagnosis			NS
Chronic hepatitis	24 (96%)	33 (86.8%)	
Compensated LC <sup>†</sup>	1 (4%)	5 (13.2%)	
ALT (IU/L)			NS
Median (range)	246 (43-614)	187 (47-1422)	
HBV DNA (pg/mL)			.065
Median (range)	442 (11.3-3590)	620 (5.1-9600)	
Previous IFN- therapy	9 (36%)	10 (26.3%)	NS
FHx <sup>‡</sup>	9 (36%)	11 (28.9%)	NS

<sup>†</sup>, Compensated liver cirrhosis; <sup>‡</sup>, Family history of chronic hepatitis B virus infection.

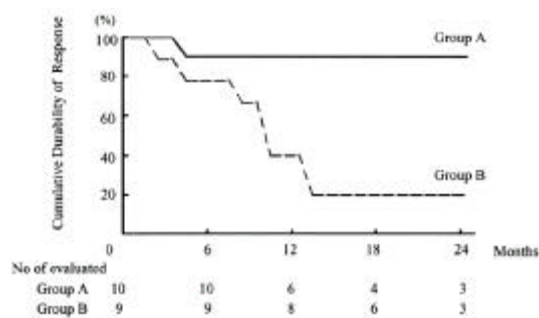
**Figure 1.** Cumulative HBeAg seroconversion rate in HBeAg-positive chronic hepatitis B patients. Cumulative HBeAg seroconversion rates at 1 year, 2 years, and 3 years during lamivudine therapy were 30.2%, 38.8%, and 42.4%, respectively.**Figure 2.** Cumulative durability of response after cessation of lamivudine therapy. The cumulative durability of response was higher in group I (HBeAg-positive/HBV DNA-positive patients) than in group II (HBeAg-negative/HBV DNA-positive patients) (64.6% vs. 33.3% at 1 year; 35.4% vs. 22.2% at 2 years; *p* = 0.079).

HBeAg		Kaplan-Meier		2. HBeAg	
				HBeAg B	
				HBeAg	
				33.8 ±	
				10.6 ( , 15-57 )	
				39.4	
				±9.9 ( , 26-61 )	
				<i>p</i> < 0.05).	
				ALT	
				246 IU/L (43-614 IU/L)	
				187 IU/L (47-1422 IU/L)	
				HBV DNA	
				442 pg/mL (11.3-3590 pg/mL)	
				620 pg/mL (5.1-9500	
				pg/mL)	

**Table 3.** Comparison of the Clinical Characteristics Between Relapsers and Nonrelapsers in HBeAg-positive Chronic Hepatitis B Patients

Variables	Relapsers (n=7)	Nonrelapsers (n=12)	<i>p</i>
Age (years)	36±9.8	31.7±11.6	NS
Sex (M/F)	7:0	11:1	NS
ALT (IU/L)			
Median (range)	274 (148-366)	230 (70-614)	NS
HBV DNA (pg/mL)			
Median (range)	344 (54.6-1740)	606.5 (122-3590)	NS
Previous IFN- therapy	3 (42.9%)	5 (41.7%)	NS
FHx <sup>†</sup>	2 (28.6%)	4 (33.3%)	NS
Duration of Therapy (months)			
Mean ±SD (range)	14±6.5 (6-24)	16.4±6.4 (6-28)	NS
Additional Therapy (months) <sup>‡</sup>			
Mean ±SD (range)	3.4±2.7 (0-7)	10±6.7 (2-26)	0.013

<sup>†</sup>, Family history of chronic hepatitis B virus infection; <sup>‡</sup>, Additional lamivudine therapy after HBeAg seroconversion.



**Figure 3.** Cumulative durability of response after cessation of lamivudine therapy in HBeAg-positive chronic hepatitis B patients. The cumulative durability of response was significantly higher in patients who received additional lamivudine therapy for more than 6 months after HBeAg seroconversion (Group A) than for less than 6 months (Group B) (90.0% vs. 40.0% at 1 year; 90.0% vs. 20.0%;  $p = 0.013$ ).

( $p = 0.065$ ).  
 9 (36%)  
 10 (26.3%)  
 , B 가  
 ( 2).

3.

12 24

1 64.6% 55.4%  
 2 12.0% 13.3% 2  
 ( $p = 0.079$ )

( 2).  
 1

38±9.8 ( , 25-51 )  
 31.7±11.6 ( , 15-57 )  
 , ALT 274  
 IU/L (148-366 IU/L) 230 IU/L  
 (70-614 IU/L)  
 HBV DNA 344  
 pg/mL (54.6-1740 pg/mL) 606.5  
 pg/mL (122-3590 pg/mL)

. HBeAg 가  
 3.4±2.7 ( , 0-7 )  
 10±6.7 ( , 2-26 )

( $p = 0.013$ ). ,  
 , B 가 ,  
 ( 3).

HBeAg B  
 HBeAg 6  
 6

**Table 4.** Adverse Events During Lamivudine Therapy

Adverse Event	Number of Patients With Adverse Events (%)
Malaise and Fatigue	12 (16.4)
Abdominal discomfort and pain	5 (6.8)
Viral respiratory infection	4 (5.5)
Chest discomfort	2 (2.7)
Headache	1 (1.4)
Fever	1 (1.7)
Pruritus	1 (1.4)
Tonsillitis	1 (1.4)
Nausea and vomiting	1 (1.4)
Indigestion	1 (1.4)
Total	29 (39.7%)

, /HBV DNA B  
 12 24 40.0% 20.0% 가 9-11  
 90.0% 90.0% 6  
 가 가  
 ( $P < 0.05$ )(3).  
 B  
 4. 2  
 .  
 Lai 17 358 B  
 (12 , 16.4%), (5 ,  
 6.8%), (4 , 5.5%), (2 , 2.7%), 16%  
 (1 , 1.4%), (1 , 1.4%), 가 (1 , 1.4%),  
 (1 , 1.4%), (1 , 1.4%),  
 (1 , 1.4%) (4). 33%  
 B HBeAg  
 12 , 24 , 36  
 30.2%, 38.8%, 42.4%  
 HBeAg 가  
 B .  
 가 가 , ALT  
 , ,  
 가 , 15-17,24,26 HBeAg /HBV DNA 가 28,  
 B HBeAg HBeAg B HBeAg  
 B 가 ALT  
 21 . 12 HBV DNA  
 HBeAg B  
 68.3% HBeAg /HBV DNA B HBeAg 가  
 70.0%  
 가 . HBeAg 가

Dienstag <sup>20</sup> HBeAg

B HBeAg 가

6

HBV DNA HBeAg 가 HBeAg B HBeAg /HBV DNA B

HBeAg B

HBeAg /HBV DNA 가 HBeAg B

B

, Santantonio HBeAg 가

<sup>20</sup> 1 ALT HBeAg B

HBV DNA HBeAg /HBV 6 가 가

DNA B 13.1 HBeAg /HBV DNA B

$\pm 3.2$  ALT HBV DNA 가

9

HBeAg B

12 24

64.6% 55.4%

HBeAg 6 : B

90.0% 가

6

12 24

40.0% 20.0%

B

<sup>19,23,25</sup>

6 가 : 1997 4

Dienstag <sup>20</sup> 1999 5 B

12 73

HBeAg 6 가 . 63 HBeAg

/HBV DNA B HBeAg HBV DNA ( 1 ) 10

12 24 HBV DNA ( 2 )

33.3% 22.2% 1 HBeAg

, 2

<sup>22</sup> : 1 2

가 12 68.3% 70.0%

1 HBeAg

12 , 24 , 36

30.2%, 38.8%, 42.4% .

12 24

1 64.6% 55.4% , 2 33.3%

22.2% ( $p = 0.079$ ). 1 HBeAg

6 6

12

24 40.0% 20.0%

90.0% ( $p = 0.013$ ). : HBeAg

/HBV DNA B HBeAg

/HBV DNA

가 , HBeAg

가 . HBeAg /HBV

DNA B

, HBeAg B

HBeAg

6 가 가 .

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: / / B ,

, HBeAg , ,

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